

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/005416

International filing date (day/month/year)
23.12.2004

Priority date (day/month/year)

International Patent Classification (IPC) or both national classification and IPC
C07K5/00, A61K38/04, A61P9/06

Applicant
ZEALAND PHARMA A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

10/584373

International application No.
PCT/GB2004/005416

1AP20 Rec'd PCT/PTO 23 JUN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/005416

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 28 - 37, 50-58

because:

- ☒ the said international application, or the said claims Nos. 50 - 58 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 28 - 37 are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/005416

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-27,38-67
	No: Claims	28
Inventive step (IS)	Yes: Claims	26-27
	No: Claims	1-25,28-67
Industrial applicability (IA)	Yes: Claims	1-49,59-67
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/005416

Re Item III.

1. Present claims 28 to 37 relate to an extremely large number of possible compounds. In particular only some structural features are given, namely "a group of a first amino acid moiety" and "a group of a second amino acid moiety", whereby one of these groups comprises a 6-membered aromatic carbon ring. However, in addition to this structural feature any further amino acid without limitation and an unlimited number of substituents can be present. In contrast to this unlimited scope of these claims support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT can only be found for a very small proportion of the compounds claimed. In particular support can be found for present claim 1 (formula (I)), and claim 15 (formula (II)) as well as the claims dependent on these two claims.
2. For the assessment of the present claims 50 to 58 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 50 to 58 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Reference is made to the following documents:

D1 : WO 03/063891 A.(HANSEN LARS BO LAURENBORG ; LARSEN BJARNE
DUE (DK); ZEALAND PHARMA AS) 7 August 2003 (2003-08-07)

D2 : WO 02/077017 A (HOLSTEIN-RATHLOU NIELS-HENRIK ; KJOLBYE ANNE LOUISE (DK); LARSEN BJARN) 3 October 2002 (2002-10-03)

D3: EP-A-0 394 989 (FUJISAWA PHARMACEUTICAL CO., LTD) 31 October 1990 (1990-10-31)

1. Although no examination will be performed for present claims 28 to 37 it is evident that claim 28 lacks novelty over the disclosure of D2 and D3 (see the passages cited in the search report)

The compounds of the general formulae (I) and (II) are structurally different from the prior compounds disclosed in D1 to D3 in particular due to the definitions of R_1 and $R_{4/5}$.

The subject matter of present claims 1 to 27 and 38 to 67 is regarded to be novel over the prior art D1 to D3 (PCT Article 33.2).

2. D1 can be regarded as representing the closest prior art since the compounds disclosed in this document are useful for the treatment of heart arrhythmia. In view of this prior art the underlying problem can be defined by the provision of further compounds showing this activity.
The alleged solution are the compounds according to present formulae (I) and (II). However, to represent a solution all compounds falling within the scope of these formulae must show this wanted activity. At least a representative amount of compounds having different structural features but falling within the scope of these general formulae should be presented and their activity has to be proven by experimental data. Such a representative number of compounds should then be the basis which allows a generalisation to the given formulae.
In the present case a generalisation of the performed tests is not possible: The compounds listed in table 1 have in common that "the 6-membered aromatic carbon ring" represents a benzyl-group. The compounds where biological data are given (see table 2) in addition have a nitro- or a methoxy-group in position 4 of the benzyl-ring.
From these data it can be concluded that the underlying problem can be regarded as

being solved for those compounds showing these structural features, namely the compounds of present claims 26 and 27. This solution is also not rendered obvious from the prior art.

Furthermore, it is evident and well-known in the art that the effect of biological active compounds is dependent on the structure of the compounds. Even small structural changes may have a strong and quite different effect on the biological activity of the compounds. This knowledge supports the fact that only the compounds falling within the scope of claims 26 and 27 can be considered to solve the underlying problem. Furthermore, the only effect of these compounds as demonstrated in table 2 lies in the antiarrhythmic activity. For such an effect an inventive step can be acknowledged. It appears that any further effect is not demonstrated and thus not verified but of speculative nature.

The subject matter of present claims 26 and 27 is thus based on an inventive step, whereas the subject matter of present claims 1 to 25, 38 to 67 is not based on an inventive step (PCT Article 33.3).

Re Item VIII.

1. Present claims 38 to 47 are not clear within the sense of Article 6 PCT due to the functional/biological features of these claims: it is not clear if only those compounds are included which show the wanted biological activities.
2. Present claims 48 and 49 do not meet the requirement of PCT Rule 6(2).
3. The use of the word "about" renders the scope of claims 10 and 11 unclear.
4. Second medical use claims 59 to 63 tries to define the therapeutic application functionally by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).